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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,049	04/01/2002	William Thomas Melvin	0380-P02753US0	4396

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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	

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12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,049	MELVIN ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,21-24 and 27-37* is/are pending in the application.

4a) Of the above claim(s) *12-19,22-24,27-29, 33-35 and 37* is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-11, 21, 30-32 and 36* is/are rejected.

7)☐ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-19, 21-24 and 27-37 are pending.

2. Applicant's election with traverse of Group I, claims 1-11, 21, 30-32 and 36 drawn to a peptide of SEQ ID NO: 1, variants, fragments, and a fusion peptide filed on 1/14/03, is acknowledged.

Upon reconsideration, Examiner has rejoin Groups II and III with Group I to cover peptide of SEQ ID NO: 2-3, variants, fragments, and a fusion peptide because SEQ ID NO: 2-3 reads on a variant of SEQ ID NO:1.

Applicant's traversal is on the grounds that the entire restriction requirement be reconsidered because the present application is a national phase application under 37 C.F.R.§ 371 and no unity of invention issue was raised during prosecution of original claims in the PCT application by either the International Search Authority or the International Preliminary Examination Authority. Further, the Examiner's reliance on Castelhano et al. has absolutely no bearing on the patentability of applicants' claims and cannot affect the special technical features, which unify the claims. Applicants argue that the 9 amino acid fragment PRPLPVAPG cited by the Examiner is not a "variant peptide" within the meaning of claim 2 because all the four reference sequences of claim 1 are 15 amino acids long. Wherein the 6 amino acids are identical with any of applicants' peptides, with respect to any of the peptides, the fragment has 9 deletions and or substitutions. Applicant argues that the fragment cited by the Examiner is not within the meaning of claims 5 or 6, because it is not a fragment of the any of the reference sequences of claim 4 (i.e. it contains amino acids APG not found in SEQ ID NOS: 1-4. Applicants argue that under PCT Rules (13.4) a product can be claimed alongside dependent claims to uses of that product, even if those uses are independently inventive. Furthermore, Applicants argue that the peptide of Group I and nucleic acids of Groups V have unity of invention because they share a special technical relationship in that the sequence of amino acids in the peptide is an essential structural element of the peptides which is encoded by an **exactly corresponding sequence of codons** in the nucleic acids. Applicants argue that the antibodies of Groups IX are also unified. This is not found persuasive because Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have a single general inventive concept and so lack unity of invention as set forth in the previous Office Action. Contrary to Applicants assertions the '208 publication teaches a variant peptide which is a variant of a fragment from 8-11 amino acids in length, which variant has three amino acid substitutions as recited in instant claim 7. Furthermore, claim 9, recites a variant peptide which is a variant of a fragment of 5-15 amino acids in length, which variant has two substitutions, which variant has one amino acid substitution. A 9 amino acid fragment with 3 substitutions meets claim 9 limitations because starting with 2 amino acids substitutions followed by one amino acid substitution results in 2 or three substations depends on where the last substitution occurs (in the substituted amino acids (2 substitutions) or in original amino acids (3 substitution)). To respond to applicants argument that

the peptides of Group I encodes an exactly corresponding sequence of codons in the nucleic acids, Examiner notes that there is no 1:1 corresponding sequence between the amino acids and the nucleic acids with respect to variant. Further, The variant DNA is not necessarily encodes peptide of SEQ ID NO:1 neither the technical feature is shared between the peptides and the nucleic acids when viewed over the prior art. Finally, Applicants are reminded that the findings and opinion of the PCT examining authority are not the controlling authority for the USPTO.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 12-19, 22-24, 27-29, 33-35 and 37 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-11, 21, 30-32 and 36 are under examination as they read on to a peptide of SEQ ID NO: 1-3, variants, fragments, and a fusion peptide.

5. This application contains an abstract form WO 00/75175 front page, however an abstract on a separate sheet is required.

6. The specification is objected to under 37 CFR 1.821(d) for failing to provide a sequence identifier for each individual sequence. Page 7, lines 17-18 has described consensus sequence, which must have a sequence identifier. Correction is required.

7. Claims 2-3 and 7-9 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form.

8. Claims 1 and 4 are objected because it is unclear whether the claims read on close or open language. It is suggested that applicant uses the phrase "consisting of" for close language and the term "comprising" for open language. However, if claims 1 and 4 were intended to read on open language, they will be rejected under 35 U.S.C. 112, first paragraph.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 5 is indefinite because a fragment of a 15 amino acids sequence cannot equal to the full 15 amino acid sequence. A fragment is incomplete sequence or part of the full peptide.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 2-9, 11, 30-32 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a peptide of SEQ ID NO:1-3 that is capable of modulating a fibrin fragment E activity, does not reasonably provide **enablement** for any variant peptide which is a variant of a peptide of SEQ ID NO:1-3 , which variant has one, two, three, or four amino acid substitutions, insertions, or deletions with respect to said peptide wherein the variant peptide is capable of modulating a fibrin fragment E activity in claim 2, wherein the variant has one or two amino acid substations, insertions, or deletions with respect to said peptide in claim 3; any fragment of SEQ ID NO: 1-3 in claim 4; any fragment of SEQ ID NO: 1-3 wherein said fragment is of 5-15 amino acids in length, wherein said fragment is from 8-11 amino acids in length, any variant peptide which is variant of any fragment of SEQ ID NO: 1-3, which variant has one, two, three, or four amino acid substitutions, insertions or deletions with respect to said fragment wherein the variant peptide is capable of modulating a fibrin fragment E activity in claim 7; any variant peptide which is a variant of a fragment of 5-15 amino acids in length of SEQ ID NO: 1-3, which variant has one or two amino acid substations, insertions or deletions with respect to said fragment wherein the variant peptide is capable of modulating a fibrin fragment E activity in claim 8, any variant peptide which is a variant of any fragment of 5-15 amino acid in length which variant has one or two amino acid substitutions, insertions or deletions, which variant has one amino acid substitution, insertion or deletion with respect to said fragment wherein the variant peptide is capable of modulating a fibrin fragment E activity in claim 9; any fusion peptide which comprises a first portion having the amino acid sequence of a peptide of SEQ ID NO: 1-3 and a second portion attached to the N- or C- terminus of the first portion, which comprises a sequence of amino acids not naturally contiguous to the first portion, said second portion comprising **any** membrane translation sequence in claims 11 and 32; any variant peptide which is a variant of a fragment of 8-11 amino acids in length of SEQ ID NO: 1-3, which variant has one amino acid substitution, insertion or deletion with respect to said fragment wherein the variant peptide is capable of modulating a fibrin fragment E activity in claim 30. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Applicant has not provided sufficient biochemical information that distinctly identifies such "variants", "fragments" and "variants of fragments" other than SEQ ID NOs:1-4. While any fibrin fragment E activity modulatory peptide may have some notion of the activity of the "inhibitory/stimulatory agent", claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make such agents, commensurate in scope with the claimed invention. The specification fails to provide any guidance on how to make any variant, any fragment, any variant of a fragment peptide or any fusion protein comprising any membrane translation sequence that can be used to stimulate cell proliferation or angiogenesis.

It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Applicant has not enabled structurally related and unrelated compounds comprising "any variant peptide/fragment" which would be expected to have difference in their activities. There is insufficient direction or objective evidence as to how to make and to how to use any peptide variant, which stimulate cell proliferation or angiogenesis for the number of possibilities associated with the myriad of direct and indirect effects associated with various cell proliferation pathways or molecules and, in turn, as to whether such a desired effect can be achieved or predicted, as encompassed by the claims. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the structure of any " peptide" or "fragment" and still provide or maintain sufficient the claimed activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Ding *et al* (J of Biol. Chem. 277:31056-31061, 2002) show that arginine to alanine substitutions within the first 21 amino acids of the carboxyl-terminal end substantially reduced the efficacy of ATE+31 on the inhibition of cell migration and angiogenesis. Similarly, Burgess *et al* (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Further, Lazar et al. (Mol Cell Biol. 8:1247-1252, 1988) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagines did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Finally, Kogan *et al.* ((J. Biol. Chem.,1995) disclose that single amino acid can determine the ligand specificity of a selectin and the unpredictable nature of amino acid alterations in adhesion/binding activity (see entire document, including the Discussion). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, insertions, substitutions and mutations of the disclosed sequence can be tolerated that will allow the peptide to function as claimed. While it is known that many amino acid substitutions are possible in any given peptide, the position

within the peptide's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the structure/function relationship. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie *et al.* Science, 247:1306-1310, 1990, p 1306, col. 2).

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view of the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

13. Claims 2-9, 11, 30-32 and 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a peptide of SEQ ID NO:1-3 that is capable of modulating a fibrin fragment E activity.

Applicant is not in possession of any variant peptide which is a variant of a peptide of SEQ ID NO:1-3 , which variant has one, two, three, or four amino acid substitutions, insertions, or deletions with respect to said peptide wherein the variant peptide is capable of modulating a fibrin fragment E activity in claim 2, wherein the variant has one or two amino acid substations, insertions, or deletions with respect to said peptide in claim 3; any fragment of SEQ ID NO: 1-3 in claim 4; any fragment of SEQ ID NO: 1-3 wherein said fragment is of 5-15 amino acids in length, wherein said fragment is from 8-11 amino acids in length, any variant peptide which is variant of any fragment of SEQ ID NO: 1-3, which variant has one, two, three, or four amino acid substitutions, insertions or deletions with respect to said fragment wherein the variant peptide is capable of modulating a fibrin fragment E activity in claim 7; any variant peptide which is a variant of a fragment of 5-15 amino acids in length of SEQ ID NO: 1-3, which variant has one or two amino acid substations, insertions or deletions with respect to said fragment wherein the variant peptide is capable of modulating a fibrin fragment E activity in claim 8, any variant peptide which is a variant of any fragment of 5-15 amino acid in length which variant has one or two amino acid substitutions, insertions or deletions, which variant has one amino acid substitution, insertion or deletion with respect to said fragment wherein the variant peptide is capable of modulating a fibrin fragment E activity in claim 9; any fusion peptide which comprises a first portion having the amino acid sequence of a peptide of SEQ ID NO: 1-3 and a second portion attached to the N- or C- terminus of the first portion, which comprises a sequence of amino acids not naturally contiguous to the first portion, said second portion comprising any membrane translation sequence in claims 11 and 32; any variant peptide which is a variant of a fragment of 8-11 amino acids in length of SEQ ID NO: 1-3, which variant has one amino acid substitution, insertion or deletion with respect to said fragment wherein the variant peptide is capable of modulating a fibrin fragment E activity in claim 30.

Applicant has disclosed only amino acid of SEQ ID NOs: 1-4; therefore, the skilled artisan cannot envision all the contemplated variant/fragment peptide sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 7 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/54208 (PTO-1449, Ref. No. N).

The `208 publication teaches a variant peptide which is a variant of 9 amino acid fragment (**PRPLPV**APG) of SEQ ID NOS: 1-3, which variant has three amino acid substitutions (APG) with respect to said fragment as claimed in instant claim 7. Further, the variant peptide meets the limitations of claim 9, because claim 9 depends from claim 8 which require a variant fragment with two amino acids substitutions and one amino acid substitution in claim 9 results in three amino acids substations.

While the prior art teachings may be silent as to the "capable of modulating a fibrin fragment E activity" per se; the product in the reference is the same as the claimed product. Therefore "capable of modulating a fibrin fragment E activity" is considered inherent property.

Since the office does not have a laboratory to test the reference variant peptide fragment, it is applicant's burden to show that the reference peptide does not modulate a fibrin fragment E activity recited in the claims. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
March 24, 2003

PATRICK J. NOLAN, PH.D.
PRIMARY EXAMINER
3/20/03